A. Lisinopril + atenolol
B. HCT+ amlodipine
C. Metoprolol + verapamil
D. Hydralazine + HCT

55. Which of the following disease states is considered a secondary cause of HTN?
A. Heart failure
B. Primary hyperaldosteronism
C. Ischemic stroke
D. Myocardial infarction

56. Which of the following tasks should NOT be delegated to nonpharmacist staff for a HTN service?
A. Making appointment reminder telephone calls to patients
B. Measuring BP and pulse
C. Developing treatment plan recommendations
D. Obtaining essential laboratory results

57. Of the following agents, which statin produces the greatest percentage change in LDL levels?
A. Pravastatin
B. Atorvastatin
C. Simvastatin
D. Rosuvastatin

58. By establishing dyslipidemia management services in the community pharmacy, pharmacists are well positioned to address which of the following patient barriers to treatment success?
A. Medication nonadherence
B. Drug interactions
C. Adverse drug reactions
D. All of the above

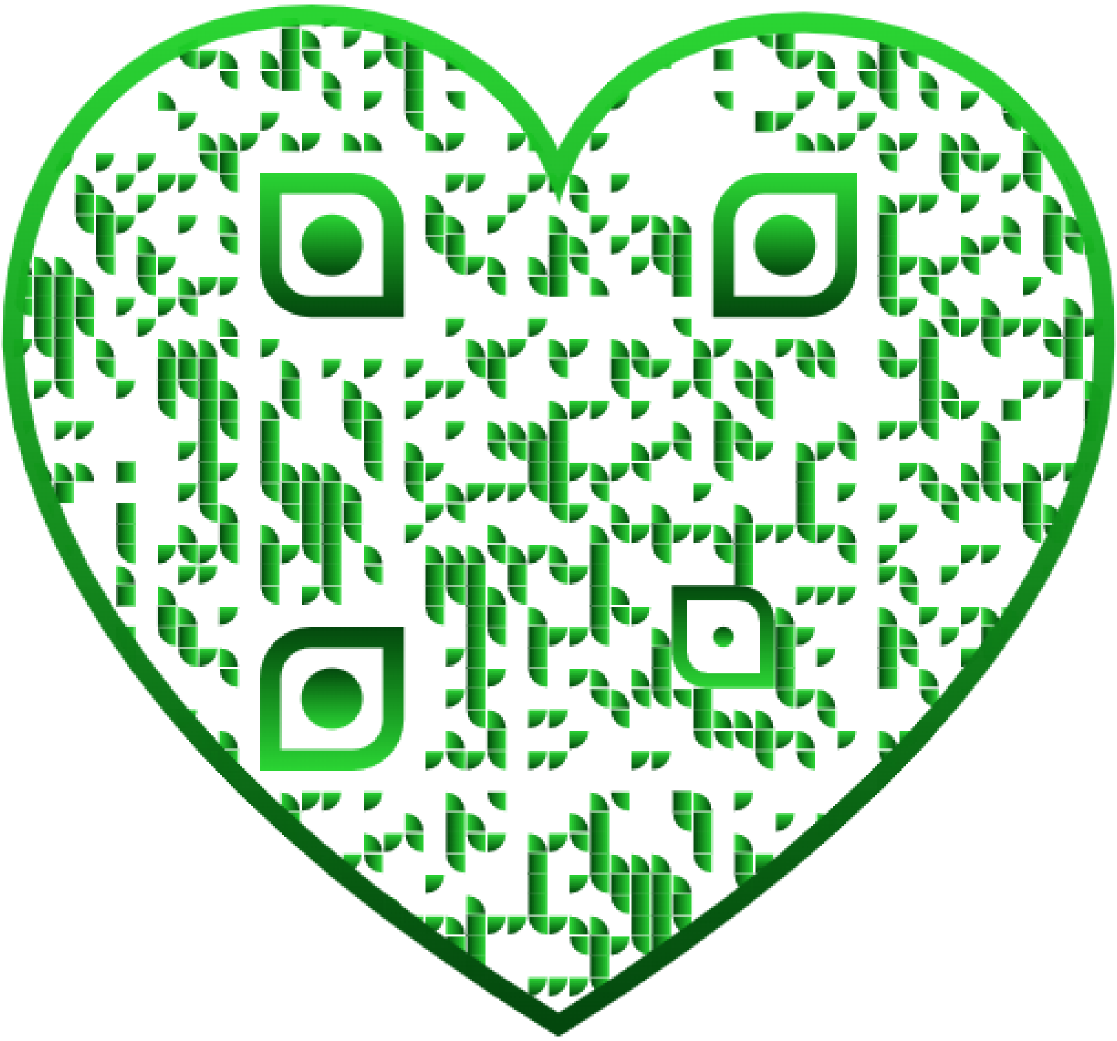
59. A 58-year-old man is admitted to the hospital with acute heart failure and pulmonary edema. Which one of the following drugs would be most useful in treating the pulmonary edema?
A. Digoxin.
B. Dobutamine.
C. Furosemide
D. Spironolactone

60. A 46-year-old man is admitted to the emergency department. He has taken more than 90 digoxin tablets (0.25 mg each), ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute, and the electrocardiogram shows third degree heart block. His serum K+ is normal. Which one of the following is the most important therapy to initiate in this patient?
A. Digoxin immune Fab.
B. Potassium salts.
C. Lidocaine.
D. Amiodarone

Question # 61 & 62 pertain to the following case:

L.R. is a 78-year-old man who presents to the emergency department for symptoms of right-sided paralysis. He states that these symptoms began about 5 hours ago and have not improved since then. He also has hypertension, benign prostatic hypertrophy, diabetes mellitus, erectile dysfunction, and osteoarthritis

61. Which is the most accurate list of L.R.'s risk factors for stroke?
A. Erectile dysfunction, age, osteoarthritis.



B. Sex, diabetes mellitus, osteoarthritis.
C. Benign prostatic hypertrophy, diabetes mellitus, age, sex.
D. Age, diabetes mellitus, sex, hypertension

62. Is L.R. a candidate for tissue plasminogen activator for treatment of stroke?
A. Yes.
B. No, he is too old.
C. No, his stroke symptoms began too long ago.
D. No, his diabetes mellitus is a contraindication for tissue plasminogen activator

63. L.R. was previously taking no drugs at home. Which choice is the best secondary stroke prevention therapy for this patient?
A. Sildenafil. B. Celecoxib. C. Aspirin. D. Warfarin

64. L.S. is a 72-year-old woman with a medical history of hypertension, type 2 diabetes mellitus, renal failure, and DVT. She presents to the anticoagulation clinic for her initial visit. Which best reflects her target INR?
A. 1.5. B. 1.75 C. 2.5. D. 3.5

65. Which of the following catecholamines is preferred as the initial agent when treating hypotension in a patient with septic shock?
A. Norepinephrine B. Dobutamine
C. Dopamine D. Phenylephrine

66. Which adverse drug effect is not observed with dobutamine?
A. Tachycardia B. Bradycardia
C. Hypotension D. Dysrhythmias

67. The therapeutic effects of digoxin include:
A. Positive inotropic, negative chronotropic, negative dromotropic
B. Positive inotropic, positive chronotropic, negative dromotropic
C. Negative inotropic, negative chronotropic, negative dromotropic
D. Positive inotropic, negative chronotropic, positive dromotropic

68. Which of the following nitrate preparations or dosage forms has the longest duration of action?
A. Sublingual nitroglycerin B. Sublingual isosorbide dinitrate
C. Oral isosorbide dinitrate D. Transdermal nitroglycerin patch

69. The side-effect of ACEi that may be minimized by switching to an angiotensin receptor blocking agent includes:
A. Orthostatic hypertension B. Dry, non-productive cough
C. Fatigue D. Hypokalemia

70. The combination of ferusemide with spironolactone can minimize ADRs like:
A. AKI B. Hyperkalemia C. Hypotension D. Gynecomastia

Questions 71–73 pertain to the following case.

E.W., a 50-year-old man (height 175 cm, weight 75 kg), presents to his primary care clinic with swelling in his entire left lower extremity, which is tender to the touch. His left calf is 6 cm larger than his right calf. He reports no recent surgical procedures. He describes mild shortness of breath, but no chest pain. He has 3+ pitting edema in his lower left leg. His medical history includes HTN, type 2 diabetes, and chronic kidney disease. His medications are metformin 1000 mg orally twice daily, empagliflozin 25 mg orally daily, lisinopril 40 mg orally daily, hydrochlorothiazide 25 mg orally once daily, atorvastatin 80 mg orally daily, and aspirin 81 mg orally daily. His initial laboratory values include Hct 40%, PT 11.2 seconds, INR 1.0, aPTT 30.0 seconds, Plt 300,000/mm3, and CrCl 50 mL/minute.

71. Which risk level most accurately reflects the clinical probability of this patient's having a DVT?
A. Low. B. Moderate. C. High. D. Very high.

72. The decision is made to initiate anticoagulation therapy and treat E.W. for DVT in the outpatient setting. What is the best recommendation for an anticoagulant initiation regimen for this patient?
A. Apixaban 10 mg PO twice daily for 7 days, then 5 mg PO twice daily.
B. Rivaroxaban 20 mg PO daily and enoxaparin 150 mg SC daily for 5 days.
C. Rivaroxaban 20 mg PO once daily.
D. Enoxaparin 100 mg SC daily and warfarin 5 mg/day PO adjusted to an INR of 2–3.

73. What is the best course of action regarding E.W.'s aspirin therapy taken for primary prevention of atherosclerotic cardiovascular disease?
A. Discontinue aspirin 81 mg orally daily.
B. Continue aspirin 81 mg orally daily.
C. Increase the aspirin dose to 325 mg orally daily.
D. Discontinue aspirin while the patient is receiving anticoagulation.

Questions 74 and 75 pertain to the following case.

C.S. is a 65-year-old woman (weight 65 kg) with a history of uncontrolled HTN, history of TIAs, and chronic NVAF. Her current medications include lisinopril 40 mg orally once daily, chlorthalidone 25 mg orally once daily, aspirin 81 mg once daily, and carvedilol 25 mg orally twice daily. Her SCr is 1.1 mg/dL and calculated CrCl is 52 mL/minute.

74. Which best describes C.S.'s CHA_2DS_2-VASc score and classification for stroke risk?
A. 2 (Moderate). B. 3 (Moderate).
C. 4 (High). D. 5 (High).

75. Which treatment for thromboembolic prophylaxis is most appropriate for C.S.?
A. Apixaban 10 mg orally twice daily for 7 days and then 5 mg orally twice daily thereafter.
B. Rivaroxaban 20 mg orally daily.
C. Edoxaban 30 mg orally once daily.

D. Warfarin 10 mg orally daily.

Questions 76 and 77 pertain to the following case.

R.P, a 60-year-old woman with HF, presents to your clinic. Her comorbidities include HTN, dyslipidemia, and a history of an ST-segment elevation MI 2 years ago. During the past year, she has had one hospitalization for decompensated HF, with significant volume overload during the hospitalization. Her current symptoms are shortness of breath when she walks more than 2 blocks from her house. She currently has no other lower-extremity edema. Other pertinent findings include blood pressure 130/80 mm Hg, heart rate 62 beats/minute, SCr 1.2 mg/dL (estimated CrCl 70 mL/minute), BUN 23 mg/dL, K 4.3 mEq/L, Na 140 mEq/L, Hgb 12.0 g/dL, and LVEF 30%. Her current medications include lisinopril 40 mg once daily, metoprolol succinate 150 mg once daily, atorvastatin 80 mg daily, and furosemide 40 mg once daily.

76. Which best describes R.P.'s current HF type, stage, and classification?
A. HFpEF, stage A, NYHA class II.
B. HFpEF, stage B, NYHA class III.
C. HFrEF, stage D, NYHA class II.
D. HFrEF, stage C, NYHA class III.

77. What is the best recommendation for R.P.?
A. Add digoxin 0.25 mg orally daily.
B. Add eplerenone 25 mg orally daily.
C. Add ivabradine 5 mg orally twice daily.
D. Add sacubitril/valsartan orally 49/51 mg twice daily.

78. A 45 – year –old man with a known hypertension and diabetes was presented to a hospital for routine follow up. He was on HCT, amlodipine, metformin and sppironolactone. The laboratory finding revealed elevated fasting blood glucose and uric acid. The medical team decided that the patient's diabetes is not well controlled and the possible rationale was linked with the drugs he takes. Which drug should be changed to control the patient's diabetes?
A. Spironolactone
B. Metformin
C. HCT
D. Amlodipine

79. A 40 – years – old woman on amlodipine and hydrochlorothiazide for regular follow - up. She was taking combined oral contraceptives and acetaminophen additionally. On examination, her blood pressure was not controlled for the last two weeks despite good adherence to her regimen. The clinical team in charge associated the poor blood pressure control with the drugs being taken. What is most likely drug that could cause a poor control in her blood pressure?
A. Combined oral contraceptive
B. Hydrochlorothiazide
C. Acetaminophen
D. Amlodipine

CHAPTER 5: RESPIRATORY DISORDERS

5.1. Asthma

Definition

- Asthma is a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, breathlessness, cough, and chest tightness, particularly at night or early in the morning. During episodes, there is variable airway obstruction, often reversible spontaneously or with treatment. There is also increased bronchial hyperresponsiveness to a variety of stimuli.
- Asthma is relieved spontaneously or with BD ± corticosteroids. It is a chronic inflammatory disease of airways where there is an ↑ed responsiveness of tracheobronchial tree

✓ *Physiologic manifestation*: AW narrowing which is usually reversible

✓ *Clinical manifestations*: a triad of paroxysms of **cough, dyspnea** and **wheezing**

Disease Pattern

1) *Episodic*: acute exacerbations interspersed with symptom-free periods
2) *Chronic*: daily AW obstruction which may be mild, moderate or severe ± superimposed acute exacerbations
3) *Life-threatening*: slow-onset or fast-onset (fatal within 2 hours)

Etiology

- ***Allergic/atopic/early onset asthma:*** rhinitis, urticaria, eczema, (+) skin tests, ↑IgE, (+) response to provocation tests with aeroallergens.
- ***Idiosyncratic/non-atopic/intrinsic asthma/late onset asthma:*** no allergic diseases, (-) skin tests, normal IgE, symptoms when upper resp infection, sx lasting days or months and usually have more severe, persistent asthma.
- ***Mixed group***: usually onset later in life

Risk Factors

Endogenous factors	Environmental factors
✓ Genetic predisposition	✓ Indoor allergens
✓ Atopy	✓ Outdoor allegens
✓ Air way hyper-responsiveness	✓ Occupational sensitizers
✓ Gender	✓ Passive smoking
	✓ Respiratory infections
	✓ Obesity

Asthma trigeres

- ***Respiratory infection:*** RSV, rhinovirus, influenza, parainfluenza, mycoplasma pneumonia
- ***Allergens:*** airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores
- ***Environment:*** cold air, fog, ozone, sulfur dioxide, nitrogen dioxide, tobacco smoke, wood smoke
- ***Emotions:*** Anxiety, stress, laughter
- ***Exercise:*** particularly in cold, dry environments
- ***Drugs/preservatives:*** Aspirin, NSAIDs, sulfites, benzalkonium chloride, nonselective β-blockers
- ***Occupational stimuli:*** Bakers (flour dust); farmers (hay mold); spice and enzyme workers; printers (arabic gum); chemical workers (azo dyes, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride); plastics, rubber, and wood workers (formaldehyde, western cedar, dimethylethanolamine, anhydrides)

Pathophysiology

- Minutes after repeated exposure, the immediate asthmatic response occurs causing bronchoconstriction whichresolves spontaneously or easily by β2-agonist use. Within 4 to 12 hours after the immediate asthmatic response, the late asthmatic response, caused by influx of inflammatory cells primarily eosinophils, Th2 lymphocytes, mast cells, macrophages, and mediators such as leukotrienes, histamine, and prostaglandin infiltrate the airβay. The reaction is often severe and prolonged and is referred to as an asthma exacerbation.
- This chronic inflammation is postulated to cause hypertrophy and hyperplasia of the bronchial smooth muscle and mucus glands which may lead to permanent, irreversible obstruction termed airway remodeling.
- The combination of airway obstruction and inflammation leads to the common symptoms of asthma which are cough (especially one that makes the patient at night), wheezing, chest tightness, and dyspnea
- ***Reduction in AW diameter***→↑AW resistance → ↓FeV and flow rates →hyperinflation →↑work of breathing →altered respiratory muscle function and elastic recoil →abnormal ventilation
- ***Vascular congestion*** and edema of bronchial walls →abnormal perfusion

Diagnosis: Clinical

- ***Episodic asthma***: Paroxysms of wheeze, dyspnoea and cough, asymptomatic between attacks.
- ***Acute severe asthma***: Upright position, use accessory resp muscles, can't complete sentences in one breath, tachypnea >25/min, tachycardia >110/min, PEF <50% of pred or best, pulsus paradoxus, chest

✍ Asthma trigeres

- ✓ ***Respiratory infection:*** RSV, rhinovirus, influenza, parainfluenza, mycoplasma pneumonia
- ✓ ***Allergens:*** airborne pollens (grass, trees, weeds), house-dust mites, animal danders, cockroaches, fungal spores
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✍ Pathophysiology

- Minutes after repeated exposure, the immediate asthmatic response occurs causing bronchoconstriction whichresolves spontaneously or easily by β2-agonist use. Within 4 to 12 hours after the immediate asthmatic response, the late asthmatic response, caused by influx of inflammatory cells primarily eosinophils, Th2 lymphocytes, mast cells, macrophages, and mediators such as leukotrienes, histamine, and prostaglandin infiltrate the airβay. The reaction is often severe and prolonged and is referred to as an asthma exacerbation.
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✍ Diagnosis: Clinical

- ***Episodic asthma***: Paroxysms of wheeze, dyspnoea and cough, asymptomatic between attacks.
- ***Acute severe asthma***: Upright position, use accessory resp muscles, can't complete sentences in one breath, tachypnea >25/min, tachycardia >110/min, PEF <50% of pred or best, pulsus paradoxus, chest

hyperresonant, prolonged expiration, breath sounds decreased, inspiratory and expiratory rhonchi.

- ***Life-threatening Features***: PEF < 33% of predicted or best, silent chest, cyanosis, bradycardia, hypotension, feeble respiratory effort, exhaustion, confusion, coma, $PaO_2 < 60$, PCO_2 normal or increased, acidosis (low pH or high [H+]).
- ***Chronic Asthma***: Dyspnea on exertion, wheeze, chest tightness and cough on daily basis, usually at night and early morning; intercurrent acute severe asthma (exacerbations) and productive cough (mucoid sputum), recurrent respiratory infection, expiratory rhonchi throughout and accentuated on forced expiration

✍ Diagnosis: Physiologic

- Demonstration of variable airflow obstruction with reversibility by means of FEV1 and PEF measurement (spirometer and peak flow meter).
  1) **FEV1** < 80% of pred – **PEF**< 80% of pred.
  2) **Reversibility**: A good bronchodilator response is a 12% or 200ml improvement in FEV_1 15min after inhalation of 200μg salbutamol (2 puffs).
  3) **Diurnal peak flow variation**: Normal variation: Morning PEF 15% lower than evening PEF. With asthma this variation is >15% (morning dipping).
  4) ***Provocation studies: AHR***
     a) **Exercise:** A 15% drop in FEV1 post exercise indicates exercise induced asthma.
     b) **Metacholine challenge**: A 20% reduction in FEV1 at Metacholine concentrations <8mg/ml indicates bronchial hyperreactivity.
        - This is expressed as a PC20 value of e.g., 0.5mg/ml (= a 20% reduction in FEV1 at 0.5mg/ml Metacholine)

✍ Management of Asthma

- **Desired Outcomes**
  a) Chronic Asthma
  (1) Prevent chronic and troublesome symptoms;
  (2) Maintain normal or near normal pulmonary function;
  (3) Maintain normal activity levels, including exercise
  (4) Prevent recurrent exacerbations of asthma
  (5) Provide optimal pharmacotherapy with minimal or no adverse effects

  b) Acute Severe Asthma
  (1) Correct significant hypoxemia;
  (2) Rapidly reverse airflow obstruction; and
  (3) Reduce the likelihood of recurrent severe airflow obstruction

Table 5.1 Asthma severity classification[1]

Components	Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent
Frequency of symptoms				
All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Throughout the day
Nighttime awakening				
≥ 12 yr	≤ 2 times/mo	3 or 4 times/mo	> 1times/wk but not nightly	Often 7 times/wk
5–11 yr				
0 – 4 yr	0	1 or 2 times/mo	3 or 4 times/mo	> 1times/wk
SABA; used for symptom control				
All ages	≤ 2 days/wk	> 2 days/wk but not daily	Daily	Several times a day
Interference with normal activity				
All ages	None	Minor limitation	Some limitations	Extremely limited
FEV1/FVC				
≥ 12 yr	Normal	Normal	Reduced 5%	Reduced > 5%
5–11 yr	> 85%	> 80%	75%–80%	< 75%
0 – 4 yr	N/A	N/A	N/A	N/A
FEV1 (% of normal)				
≥ 12 yr	> 80% (normal)	> 80% (normal)	> 60% to < 80%	< 60%
5–11 yr				
0 – 4 yr	N/A	N/A	N/A	N/A
Exacerbations requiring oral steroids				
≥ 12 yr	0 or 1/yr	≥2/yr		
5–11 yr				
0 – 4 yr	0 or 1/yr	≥2 in 6 mo or ≥4 wheezing episodes per year		

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[1] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7232/

- **Management of Chronic Asthma**

Table 5.2 Stepwise pharmacologic treatment of asthma[1]

Step	Age (yrs)	Long term controller	Quick relief
1	All ages	No controller needed	Use SABA PRN; SABA > 2 times/wk (excluding pre-exercise doses) indicates inadequate control and need to step up treatment
2	≥12	Preferred: Low-dose ICS Alternatives: LTM, theophylline, or cromolyn	
	5 – 11		
	0 – 4	Preferred: Low-dose ICS Alternatives: Montelukast or cromolyn	
3	≥12	Preferred: Low-dose ICS plus LABA *or* medium-dose ICS alone Alternative: Low-dose ICS plus LTM, theophylline or zileuton	
	5 – 11	Preferred: Low-dose ICS plus LABA *or* medium-dose ICS alone Alternative: Low-dose ICS plus LTM or theophylline	
	0 – 4	Medium-dose ICS	
4	≥12	Preferred: Medium/high-dose ICS plus LABA *and* tiotropium with history of exacerbations Alternative: Medium-dose ICS plus LTM, theophylline, or zileuton	
	5 – 11	Preferred: Medium-dose ICS plus LABA Alternative: Medium-dose ICS plus LTM or theophylline	
	0 – 4	Preferred: Medium-dose ICS plus LABA or montelukast Alternative: Medium-dose ICS plus other LTM	
5	≥12	High-dose ICS plus LABA *and* tiotropium with history of exacerbations *and* consider omalizumab with allergic asthma *and* consider IL-5 antagonist if eosinophilic asthma	
	5 – 11	Preferred: High-dose ICS plus LABA Alternative: High-dose ICS plus LTM or theophylline	
	0 – 4	High-dose ICS plus LABA or montelukast	
6	≥12	High-dose ICS plus LABA plus systemic corticosteroids *and* tiotropium with history of exacerbations *and* consider omalizumab with allergic asthma *and* consider IL-5 antagonist if eosinophilic asthma	
	5 – 11	Preferred: High-dose ICS plus LABA plus systemic corticosteroids Alternative: High-dose ICS plus LTM or theophylline plus systemic corticosteroids	
	0 – 4	High-dose ICS plus LABA or montelukast plus systemic corticosteroids	

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Table 5.3 Assessing Asthma Control in Adults and Children[1]

Components Age groups	Well Controlled	Not Well Controlled	Very Poorly Controlled
Symptoms			
≥12 yrs	≤2 days/wk	>2 days/wk	Throughout the day
5 – 11 yrs	≤2 days/wk but not >1 time each day	>2 days/wk or >1 time/day on ≤2 days/wk	
0 – 4 yrs	≤2 days/wk	>2 days/wk	
Night time awakenings			
≥12 yrs	≤ 2 times/mo	1–3 times/wk	≥ 4 times/wk
5 – 11 yrs	≤ 1 time/mo	≥ 2 times/mo	≥ 2 times/wk
0 – 4 yrs		> 1 time/mo	>1 time/wk
Interference with normal activity			
All ages	None	Some limitations	Extremely limited
SABA use for symptom control			
All ages	≤ 2 days/wk	> 2 days/wk	Several times a day
FEV1/FVC			
≥12 yrs	N/A	N/A	N/A
5 – 11 yrs	>80%	75%–80%	<75%
0 – 4 yrs	N/A	N/A	N/A
FEV1 or peak flow (of predicted/ personal best)			
≥12 yrs 5 – 11 yrs	>80%	60%–80%	<60%
0 – 4 yrs	N/A	N/A	N/A
Questionnaires ACT (range 5–25)			
>12 yr (NA for <12)	≥ 20	16–19	≤15
Exacerbations requiring oral steroids			
≥12 yrs 5 – 11 yrs	0 or 1/yr	≥2/yr	
0 – 4 yrs		2 or 3 times/yr	> 3 times/yr
Recommended action for treatment			
All ages	Maintain current step; regular follow-up every 1–6 mo; consider step-down if well controlled ≥ 3 mo	Step-up one step Reevaluate in 2–6 wk	Consider short course of oral steroids Step-up 1 or 2 steps Reevaluate in 2 wk

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[1] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7232/

- **Asthma Medications**

✓ Asthma medications are classified into two categories

  - Quick relief and
  - Long-term controller

(1) Quick relief

✓ Independent of severity, persons with asthma should have a quick relief medication readily available. The class of medication most commonly used as quick relievers is ***short-acting β_2-selective adrenergic agonists.*** They stimulate the β_2-receptor on bronchial smooth muscle to cause relaxation. All are equally effective, have an onset of action within 5 minutes, apeak at 30 to 60 minutes, and duration of 4 to 6 hours.

✓ Common side effects associated with short-acting β_2-agonists include tremor, anxiety, and tachycardia. Small dose dependent decreases in serum potassium and magnesium havebeen observed.

✓ Overuse of short-acting β_2-agonists is defined as need for medication use for symptoms of asthma more than 2 days per week or more than twice in a month for nighttime awakenings.

(2) Long-term controller medications

✓ Long-term controller medication should be evaluated for patients who over use short-acting β_2-agonists. Inhaled corticosteroids (ICSs) are the most effective drug class in helping patients achieve well-controlled asthma.

✓ Through their broad effects on gene transcription, they suppress but do not cure, multiple mediators of airway inflammation. All are equally effective at controlling bronchial inflammation and decreasing airway hyperresponsiveness; however, they are not equivalent on a microgram per microgram or puff per puff basis.

✓ In order to achieve maximum benefit, they must be used on a daily basis and education must be provided that it will take at least 2 weeks to 1 month for full effect.

✓ Common SEs of low to medium dose-ICSs are thrush and dysphonia.

> **Key Concepts** *To minimize and prevent these side effects, persons with asthma should be encouraged to rinse and spit with water after inhaler use.*

✓ If an ICS is delivered via a meter-dose inhaler (MDI), use of a spacer or holding chamber will decrease oral deposition of medication thus decreasing common side effects.

✓ At high doses over prolonged periods, patient's risk of developing adrenal suppression, osteoporosis, skin thinning, and cataract formation increases.

- ✓ To maintain a low to medium steroid dose, additional long-term medications such as long-acting β_2-agonists (LABA), leukotriene modifiers, theophylline, and/or biologic agents are added based on patient's asthma severity

(3) Others

- ✓ **LABA**: Salmeterol, formoterol
  - ➭ LABA have duration of action of approximately 12 hours.
  - ➭ Due to increased risk of death, LABAs should never be used alone for control of asthma. Especially in children and adolescents, a single inhaler which contains a LABA and inhaled steroid is recommended
  - ➭ Combination formulations available: fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, budesonide/formoterol (**Symbicort**), and mometasone/formoterol

Table 5.4 Corticosteroid dosing in asthma management[1]

Drug	Total daily dose		
	Low	Medium	High
Beclomethasone HFA 40 or 80 mcg/puff *BID dosing*	80 – 240 µg	240 – 480 µg	>480 µg
Budesonide-PG 90 or 180mcg/inhal DPI *BID Dosing*	180 – 540 µg	540 – 1080 µg	>1080 µg
Cicleosonide 80 or 160mcg/inhal *BID Dosing*	160 – 320 µg	320 – 640 µg	>640 µg
Flunisolide 80 mcg MDI *BID Dosing*	320 µg	320 – 640 µg	>640 µg
Fluticasone propionate 44, 110, 150mcg/inha DPI *BID Dosing*	88 – 264 µg	264 – 440 µg	>440 µg
Memotasone 110, 220 mcg/inhal, DPI *QD – BID Dosing*	110 – 220 µg	220 – 440 µg	>440 µg

- ✓ ***Leuketriene modifiers***
  - ➭ Leukotriene modifiers are divided into two categories to target inflammation.
  - ➭ Two antagonize the leukotriene receptor where as the original drug, Zileuton, within this class acts as a 5-lipoxygenase inhibitor.
  - ➭ Common side effects include gastrointestinal symptoms. Patients are to be monitored for behavior and mood changesand the medication

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[1] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7232/

discontinued if this occurs. Zafirlukast absorption is affected by food and zileuton may elevate liver enzymes.

- ✓ ***Theophylline*** is an adjunct option due to long-acting bronchial dilatory properties; however, it is not used often due to a narrow therapeutic range, dose-related side effects, and drug-drug interactions
- ✓ ***Omalizumab***
  - For patients who are not well-controlled despite high-dose inhaler corticosteroids, have an elevated IgE, and meet weight criteria, omalizumab may be prescribed.
  - It is a monoclonal antibody that attaches to free circulating IgE to prevent it from binding to mast cells, thus inhibiting part of the inflammatory response. It is given as a subcutaneous injection every 2 to 4 weeks. Common side effects are injection site reactions.

✍ Management of Acute Exacerbation

• Classifying Severity of Asthma Exacerbations

(1) Mild

- ✓ Dyspnea only with activity; can lie down; heart rate <100 beats/min
- ✓ Initial PEF of FEV1: >70% of predicted or personal best

(2) Moderate

- ✓ Dyspnea interferes with or limits usual activity; patient prefers sitting to lying; heart rate 100–120 beats/min
- ✓ Initial PEF of FEV1: 40 – 69% of predicted or personal best

(3) Severe

- ✓ Dyspnea at rest; interferes with conversation; sits hunched forward; agitated; heart rate > 120 beats/min
- ✓ Initial PEF of FEV1: <40% of predicted or personal best

(4) Life-threatening

- ✓ Too dyspneic to speak, perspiring; drowsy; confused
- ✓ Initial PEF of FEV1: <25% of predicted or personal best

• Management

(1) Mild to moderate exacerbation (FEV1 of 40% or more)

- ✓ Oxygen to achieve oxygen saturation (SaO_2) of 90% or more (>95% in pregnant women and those with concomitant heart disease)
- ✓ Inhaled SABA up to three doses in the first hour
  - i) Adult dose: albuterol MDI 4–8 puffs Q 20 minutes for up to 4 hours, then Q 1–4 hours as needed or by nebulizer 2.5–5 mg Q 20 minutes for three doses, then 2.5–10 mg Q 1–4 hours as needed
  - ii) Pediatric dose (12 years or younger): albuterol MDI 4–8 puffs every 20 min for three doses, then every 1–4 hrs as needed; use holding chamber (add mask if younger than 4 years) or by nebulizer 0.15

mg/kg (minimal dose 2.5 mg) every 20 minutes for three doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed

- OCS if no response immediately or if patient recently took an OCS

(2) Severe exacerbation (FEV1 of 40% or less)

- (a) Oxygen to achieve SaO_2 of 90% or more (more than 95% in pregnant women and those with concomitant heart disease)
- (b) High-dose inhaled SABA plus ipratropium by MDI plus valved holding chamber or nebulizer Q 20 min or continuously for 1 hr
- (c) Oral corticosteroids
  - (i) Adult dose: Prednisone 40–80 mg/day in one or two divided doses until peak expiratory flowreaches 70% of predicted
  - (ii) Pediatric dose (12 years or younger): 1–2 mg/kg in two divided doses (maximum 60 mg/day) until peak expiratory flow reaches 70% of predicted
- (d) Consider adjunctive therapies (IV magnesium, IV ketamine, or heliox) if the patient is still unresponsive.

(3) Impending or actual respiratory arrest

- ✓ Intubation and mechanical ventilation with oxygen 100%
- ✓ Nebulized SABA plus ipratropium
- ✓ Intravenous corticosteroids
- ✓ Consider adjunctive therapies (intravenous magnesium) if the patient is still unresponsiveto therapy.
- ✓ Admission to intensive care

✍ Outcome Evaluation

- A review of five publications on asthma control in Ethiopia revealed that the overall pooled prevalence of uncontrolled asthma to be 71.67%.[1]
- Assess onset, duration, and timing of subjective symptoms such as wheezing, shortness of breath, chest tightness, cough, nocturnal awakenings, and activity level. Use validated questionnaires (such as the Asthma Control Test, Asthma Therapy Assessment Questionnaire, or Asthma Control Questionnaire) to objectively document control.
- Monitor the use of SABAs, determine the frequency of patient exacerbations, measure lung function using office spirometry yearly or after therapeutic changes have been made in patients older than 5 years, identify environmental factors triggering asthma exacerbations, assess the patient's inhaler technique at every visit and determine adherence to long-term controller medications

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[1] Tadesse DB, Negash M, Kiros KG, Ayele E, Hailay A, Haile TG, Abay M, Demoz GT: **Uncontrolled asthma in Ethiopia: a systematic review and meta-analysis.** *Advances in respiratory medicine* 2020, 88(6):495-503.

5.2. Chronic Obstructive Pulmonary Disease (COPD)

Introduction

- Chronic obstructive pulmonary disease (COPD) is a preventable chronic disease of the airways characterized by gradual, progressive loss of lung function. COPD patients have airflow limitation that is ***not fully reversible***.
- The air flow limitation is associated with an abnormal inflammatory response of the lung to noxious particles or gases.
- *Emphysema* and *chronic bronchitis* are often present in COPD, but patients must also have abnormal spirometry to be formally diagnosed with COPD. Emphysema is an abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without fibrosis. Chronic bronchitis is inflammation of the bronchioles with mucus hypersecretion and chronic productive cough.
- A meta-analysis of five spirometry-based studies from Africa reported a mean prevalence of COPD as 13.4%, ranging from 9.4 to 22.1%.[1] A community-based study in Abeshge district, Southern Ethiopia, that defined COPD as a post-bronchodilator FEV1/FVC of less than 70%, found out a prevalence of COPD as 17.8%.[2]
- The most common risk factor for COPD is cigarette smoking; however, not all smokers develop COPD.
- Risk factors include occupational dusts and chemicals (chemical agents and fumes), indoor air pollution (wood, animal dung, crop residues, and coal burned in open fires), and outdoor airpollution.
- A rare genetic disorder called ***α-1 antitrypsin (AAT) deficiency*** is also a risk factor for COPD. Patients presenting with COPD at an early age or a strong family history should be screened for this disorder.
- Another potential risk factor is impaired lung growth during gestation, birth, and childhood.
- Oxidative stress or a depletion of antioxidants in the lungs plays a role in the development of COPD, can initiate lung inflammation and injury.

Clinical presentation

- Symptoms characteristic of COPD are dyspnea, chronic cough, and sputum production. Dyspnea is usually present every day, worsened by exertion, and progressively worsens over time. Patients describe an increased effort to breathe or gasping.

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[1] Adeloye D, Basquill C, Papana A, Chan KY, Rudan I, Campbell H: **An estimate of the prevalence of COPD in Africa: a systematic analysis.** *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2015, **12**(1):71-81.

[2] Woldeamanuel GG, Mingude AB, Geta TG: **Prevalence of chronic obstructive pulmonary disease (COPD) and its associated factors among adults in Abeshge District, Ethiopia: a cross sectional study.** *BMC pulmonary medicine* 2019, **19**(1):1-9.

> **Key Concepts** *The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define COPD as a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio of less than 0.7 in the presence of characteristics symptoms of COPD.*

- The GOLD guidelines also classify the severity of airflow limitation by reduction in postbronchodilator FEV1

Sometimes.

Table 5.5. Comparison of Asthma and COPD

	COPD	Asthma
Age	>35	Any age
Cough	Persistent and productive [illegible]	Intermittent and non-productive
Smoking	Almost invariable	Possible
Breathlessness	Progressive and persistent	Intermittent and variable
Nocturnal symptoms	uncommon unless in severe disease	Common
Family history	Uncommon unless family members also smoke	Common
Concomitant eczema or allergic rhinitis	Possible	Common

Table 5.6 Classification of COPD (Post-bronchodilator FEV1)[1]

Grade	Description	FEV1
Grade 1	Mid	>80% predicted
Grade 2	Moderate	<80% and ≥50% predicted
Grade 3	Severe	<50% and ≥30% predicted
Grade 4	Very severe	<30% predicted

✍ **Staging Acute Exacerbations of COPD**

1) **Mild (type 1):** one cardinal symptom (worsening of dyspnea, increase in sputum volume, increase in sputum prulence) plus at leas one of the following: URTI with in 5 days, fever without other explanation, increased wheezing, increased cough, increased in respiratory or heart rate >20% above baseline
2) **Moderate (type 2):** two cardinal symptoms
3) **Severe (type 3):** three cardinal symptoms

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[1] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD). 2013

chapter 5

A] less symptom.

C

COPD Classification[1]

Spirometric grade	4 3	**C** High risk Less symptoms	**D** High risk More symptoms	≥2	Exacerbations per yr
	2 1	**A** Low risk Less symptoms	**B** Low risk More symptoms	1 0	
		MMRC <2 CAT <10	MMRC ≥2 CAT ≥10		
		Symptoms			

MMRC: Modified Medical Research Counsel Dyspnea Scale; CAT: COPD Assessment Tool

Figure 5.1 COPD classification

Complications

- COPD is a progressive disease, and even with the best treatment, will worsen over time. Treatment is directed at managing symptoms or preventing exacerbations.
- The most common complication of COPD is *acute exacerbations* of symptoms.
  - ✓ A COPD exacerbation is defined as an acute change from baseline incough and/or sputum production that is beyond day-to-day variations.
  - ✓ Exacerbations affect the prognosis of COPD, lead to poor long-term outcomes, and increase mortality.
- *Pulmonary hypertension* may developdue to hypoxic vasoconstriction of the pulmonary arteries and lead to cor pulmonale.
- Additionally, *systemic features* may develop and include skeletal muscle wasting, osteoporosis, depression, cardiovascular disease, and lung ca.

Treatment

- Nonpharmacologic treatment
  - ✓ Smoking cessation is the most effective treatment for reducing the progression of COPD.
    - ➥ ***Tobacco dependence*** is a chronic condition that warrants intensive and repeated treatment with counseling and pharmacotherapy until abstinence is achieved.
  - ✓ ***Pulmonary rehabilitation*** improves exercise capacity, health-related quality of life, and survival. A comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education.

< 88 %

- ✓ **Oxygen therapy** is often necessary for COPD patients with resting hypoxemia (oxygen saturation <88% on room air).
- ✓ All patients with COPD should receive the ***influenza vaccine*** annually and the ***pneumococcal vaccine***.
- Pharmacologic Treatment
  - ✓ An approach to initial pharmacotherapy of stable COPD based on combined assessment of airflow limitation, symptom severity, and risk of exacerbations.

Table: 5.7 Initial pharmacotherapy of stable COPD.

Patient Category	First Choice	Second Choice
A (less symptoms, less risk)	SABA prn or SAMA prn	LAMA or LABA or SAMA and SABA
B (more symptoms, less risk)	LAMA or LABA	LAMA and LABA
C (less symptoms, more risk)	ICS and LABA or LAMA	LAMA and LABA or LAMA and PDE4I or LABA and PDE4I
D (more symptoms, more risk)	ICS and LABA and/or LAMA	ICS and LABA and LAMA or ICS and LABA and PDE4I or LAMA and LABA or LAMA and PDE4I

1) ***Sympathomimetics (β2-Selective Agonists)***
   - **Short-acting β_2-agonists (SABA)**: **Albuterol** inhalation aerosol and inhalation powder 1 to 2 inhalations every 4 to 6 hours
   - **Lung-acting β_2-agonists (LABA)**: Aredosed Q 12 to 24 hours on a scheduled basis and provide bronchodilation throughout the dosing interval.
     - **Salmeterol** inhalation powder 1 inhalation every 12 hours
     - **Formoterol** inhalation powder 1 inhalation every 12 hours
2) ***Anticholinergics***
   - **Short-acting muscarinic antagonists (SAMA)**
     - ***Ipratropium*** has a slower onset of action than SABA (15–20 min vs 5 min for albuterol). It may be less suitable for as-needed therapy. It has a more prolonged effect than SABA, with the peak effect occurring in 1.5 to 2 hours and the duration up to 8 hours. Inhalation aerosol 2 inhalations 4 times/day (max 12 inhalations/day).
   - **Long-acting muscarinic antagonists (LAMA)**

  - ➢ ***Tiotropium bromide*** inhalation spray 2 inhalations once daily or inhalation powder one capsule (with 2 inhalations) once daily
- ⇘ **Combination** Anticholinergics and Sympathomimetics
  - ➢ Ipratropium plus albuterol inhalation

3) *Methylxanthines*

- ⇘ ***Theophylline*** and *aminophylline* produce bronchodilation by inhibiting PE and other mechanisms.
- ⇘ Methylxanthines have a very limited role in COPD therapy because of drug interactions and interpatient variability in dosage requirements

4) *Corticosteroids*

- ⇘ Corticosteroids reduce capillary permeability to decrease mucus, inhibit release of proteolytic enzymes from leukocytes, and inhibit PGs.
- ⇘ Appropriate situations for corticosteroids in COPD include
  1. Short-term systemic use for acute exacerbations and
  2. Inhalation therapy for chronic stable COPD in select patients.
- ⇘ Chronic systemic corticosteroids should be avoided in COPD management because of questionable benefits and high risk of toxicity.

5) *Phosphodiesterase Inhibitors*

- ⇘ **Roflumilast** is a phosphodiesterase 4 (PDE4) indicated to reduce risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
- ⇘ The dose is 500 mcg orally once daily, with or without food

- Treatment of Exacerbations of COPD: antimicrobial therapy if symptoms suggest (1) increased dyspnea; (2) increased sputum volume; and (3) increased sputum purulence – macrolides, 3rd generation cephalosporin, doxycycline
  - ⇘ Levofloxacin: 500mg PO/IV q24hr X 5 days
  - ⇘ Moxifloxacin: 400mg PO/IV q24hr X 5 days
  - ⇘ Clarithromycin: 500mg PO q12hr X 7 days
  - ✓ Bronchodilators: short acting β2 agonists are preferred
  - ✓ Corticosteroids: use is well established in COPD exacerbation
    - ⇘ Prednisone 30 – 40mg PO QD X 14 days

✍ **Outcome evaluation:** Follow up every 3 to 6 months to assess effectiveness and safety of therapy. Review smoking status, symptoms, exacerbation frequency and severity, and medication regimen, annual spirometry to assess decline in lung function

REVIEW QUESTIONS

Questions 1–3 pertain to the following case:

A 23-year-old woman has been coughing and wheezing about twice weekly, and she wakes up at night about three times per month. She has never been given a diagnosis of asthma and has not been to a physician, she says, "in years." She uses her roommate's salbutamol inhaler, but having recently run out of refills, she is seeking care. Her activities are not limited by her symptoms. Spirometry today reveals FEV1 82% of predicted.

1. According to the current guidelines, which is the best classification of her asthma?
   A. Intermittent.
   B. Mild persistent.
   C. Moderate persistent.
   D. Severe persistent.
2. Which medication is best to recommend for her, in addition to salbutamol MDI 1 or 2 puffs every 4–6 hours as needed?
   A. No additional therapy needed.
   B. Oral montelukast 10 mg/day.
   C. Mometasone DPI 220 mcg/puff 1 puff daily.
   D. Budesonide/formoterol MDI 80/4.5 mcg per puff 2 puffs twice daily
3. At first, the patient's symptoms were well controlled on your recommended therapy. However, when winter arrived, her symptoms were no longer well controlled, and she started using her albuterol 3 or 4 days per week during the day. Which is the preferred treatment change?
   A. No change in therapy is needed.
   B. Switch to budesonide/formoterol MDI 160/4.5mcg/puff 2 puffs BID.
   C. Add montelukast orally 10 mg daily.
   D. Increase mometasone DPI to 220 mcg/puff 2 puffs daily.
4. An 8-year-old boy has been having daytime asthma symptoms once or twice weekly and is awakened twice weekly at night with coughing. In addition to albuterol MDI 1 or 2 puffs every 4–6 hours as needed, which is the best initial therapy for him?
   A. Fluticasone MDI 44 mcg/puff 1 puff twice daily.
   B. Fluticasone MDI 110 mcg/puff 1 puff twice daily.
   C. Fluticasone/salmeterol DPI 100/50 mcg per puff 1 puff twice daily.
   D. Oral montelukast 10 mg/day
5. Two asthmatic pateints X and Y were undergone with metacholin challenge to see airway hyperresponsiveness. X was found to have a PC 20 of 0.5mg/ml where as Y had 0.25 mg/ml. In this regard:
   A. Y is more hyperresponsive to metacholin than X
   B. X and Y have the same respiratory the same respiratory response for metacholin

C. X's FEV1 will be much lower than Y's FEV1 for the same concentration of metacholin
D. Metacholin causes bronchodilation which increases FEV1 in these patients

6. Drugs which are the *corner stone* in the management of chronic asthma are
A. SABA B. LABA C. ICS D. OCS

7. A 70-year-old woman has persistent shortness of breath, cough, and sputum production that has gradually worsened during the past year. Her COPD assessment test score is 12. She has been using albuterol HFA two inhalations several times per day for persistent shortness of breath. Her spirometry showed a forced expiratory volume in 1 second (FEV1) equal to 70% of predicted and an FEV1/forced vital capacity (FEV1/FVC) equal to 60% of predicted after a bronchodilator. Her blood eosinophil count is 50 cells/mm3. She has never had a COPD exacerbation. Which is the best medication to initiate?
A. Tiotropium DPI. B. Beclomethasone MDI.
C. Montelukast orally. D. Fluticasone plus salmeterol MDI.

8. Which one of the following practices is advisable when patients use their inhalers?
A. Breath in before pressing their inhalers
B. Breath in through their nose as they press down on the inhaler
C. Breathing several times for a puff
D. They should breath in as they press down on inhaler

9. Advantages of spacer devices include all of the following except:
A. Enhanced lung delivery
B. Decreased oropharyngeal deposition of drug
C. Increased percent of drug particles achieving respirable droplet size
D. Standardization of spacers to make them substitutable

Question # 10 and 11: A 37-year-old female presents with the following: FEV_1 76% predicted, use of albuterol (for rescue) 5-6 days/week, waking with asthma symptoms 4-5 times/month, and increased asthma symptoms during her daily walk to work and workouts.

10. Her asthma severity would be classified as:
A. Intermittent B. Mild C. Moderate D. Persistent

11. Preferred therapy options for this patient would be:
A. SABA prn plus short course OCS
B. SABA prn plus low dose ICS/LABA
C. SABA prn plus medium dose ICS/LAMA
D. SABA prn plus high dose ICS

12. Which one of the following is not a mediator associated with airway inflammation?
A. Histamine B. Goblet cells C. Leukotrienes D. Prostaglandins

13. Which of the following statements is **correct** concerning ICS in the treatment of asthma?
    A. Available ICS are equipotent based on a mcg to mcg comparison
    B. Advantages are high topical potency and low systemic activity
    C. Response to therapy is prompt, with resolution of symptoms within 3-4 days
    D. Therapeutic index is irrelevant to the delivery device
14. Which of the following medications is **not** associated with triggering of asthma symptoms?
    A. Aspirin B. Naproxen C. Propranolol D. Penicillin
15. The pharmacist's important contributions to the asthma management team include all of the following except:
    A. Gathering complete, updated medication histories.
    B. Performing comprehensive physical exams.
    C. Inhaler and device training.
    D. Environmental trigger education
16. GB is a 42-year-old male with asthma, GERD, and hypertension. He states that he has increased the use of his albuterol inhaler before bedtime and notices it mostly after he eats later and larger meals than usual for business dinners. What should the pharmacist do?
    A. Increase his albuterol to scheduled nighttime use.
    B. Increase his maintenance ICS to high dose.
    C. Assess GERD symptoms and suggest nonpharmacologic or over-the-counter therapy.
    D. Immediately refer to asthma specialist since GB's asthma is no longer controlled.
17. A 9-year-old girl has severe asthma, which required three hospitalizations in the last year. She is now receiving therapy that has greatly reduced the frequency of these severe attacks. Which of the following therapies is most likely responsible for this benefit?
    A. Albuterol by aerosol. B. Ipratropium by inhaler.
    C. Fluticasone by aerosol. D. Theophylline orally.
18. Which of the following products, when taken with theophylline, can decrease theophylline's serum drug levels?
    A. Caffeine B. Diphenhydramine C. Cigarette D. Tea

Questions 19–20 pertain to the following case:

A.S. is a 23-year-old woman who has been wheezing and coughing for the past year. In the past few months, she has used her albuterol inhaler about four times daily during the day and about twice weekly for coughing that awakens her during the night. Spirometry is consistent with an asthma diagnosis.

19. Which best classifies A.S.'s asthma severity?
    A. Intermittent. B. Mild persistent.
    C. Moderate persistent. D. Severe persistent.
20. Which is the best controller therapy for A.S.'s asthma?
    A. Fluticasone (110 mcg/actuation) two inhalations twice daily by MDI.
    B. Montelukast 10 mg 1 tablet orally daily.
    C. Salmeterol 1 inhalation (50 mcg) twice daily by DPI.
    D. Budesonide/formoterol (160 mcg/4.5 mcg) 1 inhalation BID by MDI.

Questions 21–22 pertain to the following case:

BT, a 23-year-old woman, has been coughing and wheezing about twice weekly, and she wakes up at night about three times per month. She has never been given a diagnosis of asthma, and she has not been to a physician "in years." She uses an old albuterol inhaler but recently ran out, so she is seeking care. Her activities are not limited by her symptoms.

21. Spirometry is done today, and B.T.'s FEV1 is 82% of predicted. Which is the best classification of her asthma?
    A. Intermittent. B. Mild persistent.
    C. Moderate persistent. D. Severe persistent.
22. In addition to albuterol MDI 1 or 2 puffs every 4–6 hours as needed, which medication is best to recommend for B.T?
    A. No additional therapy needed.
    B. Montelukast orally 10 mg daily.
    C. Mometasone HFA 200 mcg/puff, 1 puff daily
    D. Budesonide/formoterol 80/4.5 mcg/puff, 2 puffs twice daily
23. An 8-year-old boy has had daytime asthma symptoms once or twice weekly and is awakened twice weekly during the night with coughing. In addition to albuterol MDI 1 or 2 puffs every 4–6 hours as needed, which is the best initial therapy for this patient using 2020 Focused Updates?
    A. Fluticasone HFA 44 mcg/puff, 1 puff twice daily.
    B. Montelukast 10 mg daily.
    C. Fluticasone/salmeterol 100/50 mcg/puff, 1 puff twice daily.
    D. Budesonide/formoterol 80/4.5 mcg/puff, 1 puff twice daily.

Questions 24 and 25 pertain to the following case:

TM, a 62-year-old was recently given a diagnosis of COPD. Spirometry shows he has an FEV1/FVC 60%, pre-bronchodilator FEV1 70% of predicted, and post-bronchodilator FEV1 72% of predicted. His symptoms are very bothersome. He is walking slower than others because of shortness of breath and is having to stop to catch his breath every so often when walking on level ground (Modified Medical Research

Council = 2). He had one exacerbation in the past year without hospitalization.

24. According to the GOLD guidelines, which is the most appropriate grade and patient group classification for T.M.?
    A. Grade 2, group A.
    B. Grade 2, group B.
    C. Grade 3, group C.
    D. Grade 3, group D.
25. In addition to albuterol HFA 2 puffs every 4–6 hours as needed, which pharmacotherapy option is most appropriate to initiate for T.M.?
    A. No additional therapy needed.
    B. Formoterol solution 20 mcg: Inhale solution twice daily.
    C. Salmeterol/fluticasone 50/500 one inhalation twice daily.
    D. Salmeterol/fluticasone 50/500 one inhalation twice daily plus roflumilast 250 mcg orally once daily.

CHAPTER 6: HEMATOLOGIC DISORDERS

6.1. Anemia

✍ Definition

- Anemia is a reduction in either the concentration of Hb or RBCs, that results in reduced oxygen-carrying capacity of the blood. Anemia is defined by the WHO as Hgb <13 g/dL in men or <12 g/dL in women. Anemia can result from inadequate RBC production, increased RBC destruction, or blood loss. It can be a manifestation of a host of systemic disorders, such as infection, chronic renal disease, or malignancy

✍ Epidemiology

- Anemia affects a large part of the world's population. According to the WHO, almost 1.6 billion people (25% of the world's population) are anemic. Iron deficiency is the leading cause of anemia worldwide, accounting for as many as 50% of cases. Patients with specific comorbidities such as cancer and chronic kidney disease (CKD) have significantly higher rates of anemia

✍ Anemia Classification by RBC Size

a) **Macrocytic**: Vitamin B_{12} and folic acid deficiency
b) **Normocytic:** recent blood loss and chronic disease.
c) **Microcytic:** Iron deficiency

✍ Clinical Presentation

- **Symptoms**: decreased exercise tolerance, fatigue, dizziness, irritability, weakness, palpitations, vertigo, shortness of breath, chest pain, neurologic symptoms in vitamin **B_{12}** deficiency
- **Signs**: tachycardia, pale appearance (most prominent in conjunctivae), ↓ed mental acuity, increased intensity of some cardiac valvular murmurs, diminished vibratory sense or gait abnormality in vitamin B_{12} deficiency

✍ Laboratory Tests

(1) Hemoglobin

- ✓ Normal: Male, 14 to 18 g/dL; females, 12 to 16 g/dL
- ✓ The amount of Hb per volume of whole blood
- ✓ Higher value in males: stimulation of RBC production by androgenic steroids,
- ✓ Lower values in females: result of blood loss during menstruation.

(2) Hematocrit

- ✓ Normal: Males, 39% to 49%; females, 33 to 43%
- ✓ The actual volume of RBCs in a unit volume of whole blood (%)
- ✓ A low Hct indicates a reduction in either the number or the size of RBCs or an increase in plasma volume.

(3) Red Blood Cell Count

- ✓ Normal: males, 4.3 to 5.9 × 10^6/mm^3; female, 3.5 to 5.0 × 10^6/mm^3
- ✓ The RBC count is an indirect estimate of the Hb content of the blood
- ✓ It is an actual count of RBCs per unit of blood.

(4) Red Blood Cell Indices

- ✓ Are calculated from the Hb, Hct, and RBC count
- ✓ Describe the size and Hb content of the RBCs
- ✓ MCV, MCH and MCHC

i) **Mean Cell Volume (MCV)**

- ✓ Hct/RBC Count
- ✓ Average volume of RBCs
- ✓ **Macrocytic**: size is larger than normal (Folic acid and vitamin B_{12} deficiency)
- ✓ **Microcytic**: size is smaller than normal (IDA and thalassemia)
- ✓ **Normocytic**: size is within normal limits
- ✓ When IDA (decreased MCV) is accompanied by folate deficiency (increased MCV), the overall MCV may be normal

ii) **Mean Cell Hemoglobin (MCH):**

- ✓ Hb/RBC Count
- ✓ It is the amount of Hb in a RBC
- ✓ **Low MCH**: 2 morphologic changes, microcytosis and hypochromia
  - ➯ A microcytic cell contains less Hb b/se it is a smaller cell
  - ➯ A hypochromic cell has a low MCH b/se of the ↓ed concentration of Hb present in the cell
- ✓ **High MCH**: macrocytosis (vitamin B_{12} or folate deficiency)

iii) **Mean Cell Hemoglobin Concentration (MCHC)**

- ✓ Hb/Hct: The concentration of Hb per volume of cells
- ✓ MCHC is independent of cell size,
  - ➯ It is more useful than MCH in distinguishing between microcytosis and hypochromia
  - ➯ A low MCHC indicates hypochromia;
  - ➯ A microcyte with a normal Hb concentration will have a low MCH but a normal MCHC.
- ✓ A decreased MCHC is seen most often in IDA.

(5) Total Reticulocyte Count: Normal 1%.

- ✓ It is an indirect assessment of new RBC production. It reflects how quickly immature RBCs are produced by bone marrow and released into the blood. High reticulocyte count: *acute blood loss* or *hemolysis*. A lack of reticulocytosis in anemia indicates: iron deficiency, B12 deficiency, anemia of chronic disease (ACD), malnutrition, renal insufficiency, and malignancy.

(6) Serum Iron

- ✓ Serum iron is the concentration of iron bound to transferrin. Transferrin is normally about one-third bound (saturated) to iron. The serum iron level decreases with **IDA** and **ACD** and increases with **hemolytic anemias** and **iron overload**.

(7) Serum ferritin: Ferritin is the protein-iron complex found in macrophages used for iron **storage**; low in IDA

(8) Total Iron-Binding Capacity (TIBC)

- ✓ TIBC usually is higher when body iron stores are low. The finding of a **low serum iron level** and a **high TIBC** suggests IDA. Decreased TIBC and a decreased serum iron level: ACD

(9) Homocysteine

- ✓ **VitaminB_{12}** and **folate** both are required for conversion of **homocysteine** to **methionine.** Increased serum homocysteine may suggest vitamin B_{12} or folate deficiency. Homocysteine levels also can be elevated in patients with vitamin B_6 deficiency, renal failure, hypothyroidism, or a genetic defect in cystathionine β-synthase

(10) Methylmalonic Acid

- ✓ A vitamin B_{12} coenzyme is needed to convert methylmalonyl coenzyme A to succinyl coenzyme A. Patients with vitamin B_{12} deficiency have increased concentrations of serum methylmalonic acid (MMA), which is a more specific marker for vitamin B_{12} deficiency than homocysteine.

A) Iron-Deficiency Anemia

✍ Introduction

- Iron deficiency is the most common nutritional deficiency. Pregnancy requires an additional 700 mg of iron.

> **Key Concepts** *Iron is best absorbed in its ferrous (Fe^{2+}) form. The normal daily diet contains mainly the ferric (Fe^{3+}) non-absorbed form. After iron is ionized by stomach acid and then reduced to the Fe^{2+} state, it is absorbed primarily in the duodenum, and to a smaller extent in the jejunum, via intestinal mucosal cell uptake.*

- The daily recommended dietary allowance is 8 mg in adult males and postmenopausal females and 18 mg in menstruating females.
- Heme iron, which is found in meat, fish, and poultry, is about three times more absorbable than the nonheme iron found in vegetables, fruits, dried beans, nuts, grain products, and dietary supplements.
- Gastric acid and other dietary components such as ascorbic acid increase the absorption of nonheme iron. Dietary components that form insoluble complexes with iron (phytates, tannates, and

phosphates) decrease absorption. Phytates, a natural component of grains, brans, and some vegetables, can form poorly absorbed complexes. This partially explains the increased prevalence of IDA in poorer countries, where grains and vegetables compose a disproportionate amount of the normal diet. Polyphenols bind iron and decrease nonheme iron absorption when large amounts of tea or coffee are consumed with a meal.

✍ **Etiology**

- Iron deficiency results from prolonged negative iron balance; increased iron demand or hematopoiesis, increased loss, or decreased intake/absorption
- Higher risk for iron deficiency includes children younger than 2 years, dolescent girls, pregnant/lactating females, and those older than 65 years

✍ **Labs**

- Low serum iron and ferritin levels and high TIBC, Hb and Hct fall below normal values, A microcytic hypochromic anemia develops (MCV is reduced)

✍ **Treatment**

- Desired Outcomes
  - ✓ Reversal of hematologic parameters to normal,
  - ✓ Return of normal function and quality of life,
  - ✓ Prevention or reversal of long-term complications
- Dietary Supplementation
  - ✓ Iron is best absorbed from meat, fish, and poultry.
  - ✓ Orange juice and other ascorbic acid-rich foods can be included with meals to increase absorption.
  - ✓ Milk & tea reduce absorption
- Oral Iron Preparations
  - ✓ In most cases of IDA, oral administration of iron therapy with soluble Fe^{2}+ iron salt is appropriate.
  - ✓ For patients with IDA, the generally recommended dose is about 150 to 200 mg of elemental iron daily, usually in two or three divided doses to maximize tolerability

✓ Adverse reactions to therapeutic doses of iron are

- ➪ Primarily GI in nature and consist of dark discoloration of feces, constipation or diarrhea, nausea and vomiting
- ➪ GI side effects usually are dose related and are similar among iron salts when equivalent amounts of elemental iron are administered.

Table 6.1 Oral iron preparations[1]

Iron salt	% of elemental Fe	Formulation and elemental iron provided
Ferrous sulfate	20	60-65 mg/324-325 mg tab 60 mg/5 mL syrup 44 mg/5 mL elixir 15 mg/1 mL
Ferrous sulfate (exciccated)	30	65 mg/200 mg tab 50 mg/150 mg tab
Ferrous gluconate	12	38 mg/ 325 mg tab 28-29 mg/240-246 mg tab
Ferrous fumarate	33	66 mg/200 mg tab 106 mg/324-325 mg tab

- Parenteral Iron Therapy
  - ✓ Indications for parenteral iron therapy include intolerance to oral, malabsorption, long-term nonadherence, patients with significant blood loss, CKD patients, cancer patients receiving chemotherapy (on ESAs)
  - ✓ Four different parenteral iron preparations: Iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol

B) Megaloblastic Anemias

- Macrocytosis is caused by abnormal DNA metabolism resulting from vitamin B_{12} or folate deficiency. It also can be caused by administration of various drugs, hydroxyurea, zidovudine, cytarabine, methotrexate, azathioprine, 6-mercaptopurine, cladribine

✍ ***Vitamin B_{12} Deficiency Anemia***

- Inadequate dietary consumption of vitamin B_{12} is rare. It usually occurs only in patients who are strict vegans and their breast-fed infants, chronic alcoholics, and elderly patients who consume a "tea and toast" diet because of financial limitations or poor dentition.
- Decreased vitamin B_{12} absorption can occur with loss of intrinsic factor by autoimmune mechanisms (pernicious anemia, in which gastric parietal cells are selectively damaged), chronic atrophic gastritis, or stomach surgery. Vitamin B_{12} deficiency can cause neurologic and hematologic complications.
  - ✓ These usually start with bilateral paraesthesia in extremities; deficits in proprioception and vibration
  - ✓ If not treated, this can progress to ataxia, dementia-like symptoms, psychosis, and vision loss.

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[1] Cook KM, Greer DM. Anemias. In: DiPiro JT, Yee GC, Haines ST, Nolin TD, Ellingrod VL, Michael Posey LL. eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e. McGraw Hill; 2023. Accessed January 24, 2023.